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A CONTRIBUTION TO THE BOTANY OF THE ORGANISM OF BLASTOMYCOSIS.*

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Through the kindness of Dr. Charles A. Powers, I have been able during the past year to study the lesions from a fatal case of systemic blastomycosis, and certain of my observations seem to have an important bearing on the disputed questions in regard to botanical relations of the organism. Briefly, I believe that I have observed the ascus of the organism, and that I have thus been enabled to determine the true botanical position of the plant within fairly well defined limits—limits which, it is hoped, will be still more sharply defined by the results of further observations now in progress.

A brief review of the history of the controversy will best serve to define the questions at issue.

The first authentic case of blastomycosis was studied and reported independently by Busse[1] and by Buschke[2] in 1894–6. In 1898 Gilchrist[3] and Stokes reported the first American case. The organisms in these cases presented certain differences, and are probably not identical. That of Busse and Buschke has been assigned to the saccharomycetes by De Beurmann and Gougerot.[4] Gilchrist and Stokes called their organism blastomyces because it was found in the lesions as a yeastlike cell which quite obviously multiplied by budding. This term, which has come to be almost universally employed in this connection, was offered only as a temporary makeshift by Gilchrist and Stokes, and is highly objectionable because the presence or absence of budding forms has little or no biological significance, such forms being found widely distributed among the fungi. It has long been abandoned by mycologists, in any save a purely morphological sense; the yeasts, which

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* Received for publication, June 2, 1913.

[1] *Centralbl. f. Bakteriol.*, 1896, 16, p. 175; *Virch. Arch.*, 1895, 140, p. 23; *Ibid.*, 1896, 144, p. 360.

[2] *Volkmann's Samml. klin. Vortr.*, N. F., 1898, No. 218 (Chir. No. 64, p. 1081); *Arch. f. Dermat. u. Syph.*, 1899, 47, p. 261.

[3] *Jour. Exper. Med.*, 1898, 3, p. 53.

[4] *Les nouvelles mycoses*, Paris, 1912.

are perhaps especially characterized by this mode of reproduction, being now designated as saccharomyces—a designation of course, which is based on quite another property.

As indicating that the term blastomycosis was regarded as inaccurate (and therefore undesirable), even very early in the discussion of the disease, Bassoe[1] may be cited:

> "I have used the term blastomycosis with considerable misgiving, as I am aware that there is a tendency among botanists to designate as blastomycetes the budding forms of any fungi which otherwise may not at all belong together. For the present the term blastomycosis is used for lack of a better one, and in order to emphasize the fact, so important from a medical standpoint, that we are dealing here with an infection by organisms which bud in the tissues of the human body."

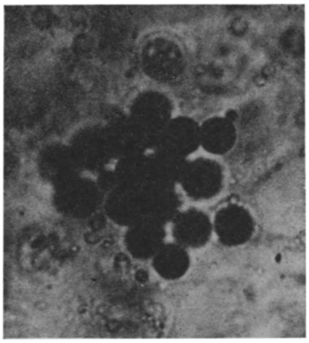

FIG. 1.—High magnification. Half-grown spores, showing possible budding.

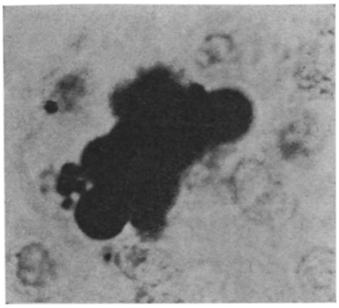

FIG. 2.—High magnification. Half-grown spores, showing possible budding.

Granted that the budding process has no biological significance, it is difficult to understand in what its importance consists. Any morphological feature is important so long as it remains an individual and peculiar characteristic. Its importance diminishes from the diagnostic standpoint in proportion as it becomes common to a wide variety of organisms. Indeed there is apparently ample ground for the view that the term blastomycosis really includes a wide variety of organisms. Cultures from different cases present considerable variations in morphology and cultural characteristics, and certain cases are marked by the great abundance on the one hand, or absence on the other, of budding forms. The well known fact that certain cases recover rapidly under potassium iodide, while others progress obstinately in spite of it, points in the same direction. The differentiation of these types (if indeed differences exist) is bound to remain a practically unsolved problem until the way is found to study these plants in their natural habitat. According to De Beurmann and Gougerot,[1] the immuno-diagnostic reactions fail to differentiate some of these conditions.

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[1] *Jour. Infect. Dis.*, 1906, 3, p. 91.

In 1901 Ricketts[2] made a detailed study of an extensive series of cases, and came to the conclusion that the organism is an oïdium, basing his opinion on the abundant formation of spores of the oïdium type (conidea) in cultures; while Ophüls[3] preferred the designation coccidioides or coccidioidal oïdiummyces. Ophüls believes, on somewhat inadequate grounds, that the disease observed by him in California is not identical with the "Chicago disease." However this may be, these two terms seem to be slowly replacing the older designation in this country. But multiplication by means of coccidia is not confined to Linck's oïdium. On the contrary, like the formation of yeastlike bodies, it is widely distributed among the molds. For this reason both Ricketts and Ophüls regarded their suggestions as anything but final. The discovery of a higher type of fruit organ (sporangium, ascus) would serve at once to remove the plant from the oïdium group, and to place it finally and definitely in its proper position.

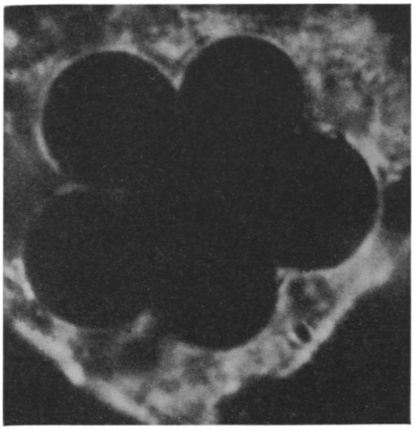

FIG. 3.—High magnification. Group of fully developed spores.

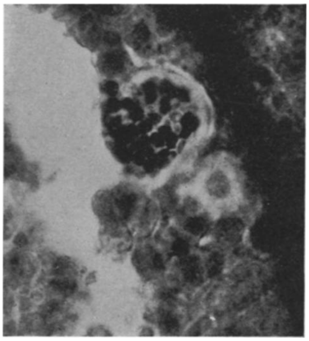

FIG. 4.—Medium magnification (about 700×). Ascus with spores some of which are just escaping from the sac.

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[1] *Loc. cit.*

[2] *Jour. Med. Res.*, 1901, 1, p. 373.

[3] *Jour. Am. Med. Assn.*, 1905, 45, p. 1291.

In 1909 De Beurmann and Gougerot[1] made an exhaustive comparative study of the "blastomycetic" organisms and arrived at the following classification, based on the mycologic system of Van Tieghem. According to this system the exoasces are a family of the discomycetes. De Beurmann and Gougerot say: "Under the term exascoses we include all the mycoses due to parasites known to belong to the botanical group exoasces, or which can be assimilated to it" (by analogy). The following grouping of cases is thus arrived at:

1. (*a*) *Saccharomyces*, typical yeasts, and *Atelosaccharomyces*, yeasts in which ascus production has not been observed.—This group includes a number of isolated cases, the most important of which, for our purpose, is the case of Busse and Buschke, already cited, the organism of which was assigned to the yeasts by Vuillemain and Guìguên, and called cryptococcus.

(*b*) *Parasaccharomyces*.—An organism closely related to the yeasts, as the name implies, but presenting characteristics indicating that it is a transitional form between the yeasts and endomyces.

2. *Zymonema*.—A new genus proposed by De Beurmann and Gougerot. The name indicates that the plant shows mixed characters, namely, yeast forms and mycelial threads. It includes the cases variously designated as blastomycosis, oïdiomycosis, coccidioidosis, and Chicago disease. These cases cannot be properly assigned to either the first or the third group.

3. *Endomyces*.—The organism of thrush, formerly called *oïdium albicans*, which has now been definitely shown to be an endomyces, not an oïdium.

According to De Beurmann and Gougerot this classification is final with the single exception of the proposed new second group, *Zymonema*. The last is frankly placed here by analogy, in the expectation that the character of the ascus, when discovered, will justify its remaining in this place.

Cultures from the case placed at my disposal by Dr. Emery have been grown on various media, and have been observed from time to time for about one year, without disclosing more than what numerous other observers have recorded. One finds the mycelial threads septate and branching at irregular intervals; chlamydospores; conidiospores, forming either at the ends of the hyphae, or in continuity, the conidiospores in chains and separated by septa, in which case they represent the oïdium type of spore formation. The conidiospores are at first elongated. Later they become more and more spherical, and are finally set free to become, apparently, the yeast cell bodies from which the organism derived its earliest name. It is worth noting that the conidium-bearing hyphae are larger and denser than the vegetative threads.

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[1] *La tribune medicale*, 1909, 42, pp. 501, 517, also *loc. cit.*

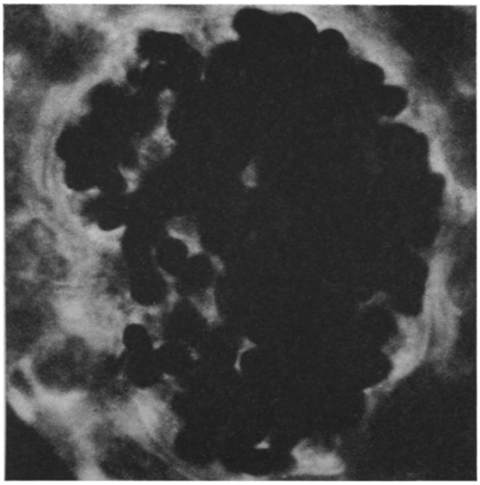

FIG. 5.—High magnification (about 3500×). Fully developed ascus with spores. The sac appears as a refractile membrane, which is not in perfect focus in certain regions.

Irons and Graham[1] observed in unstained preparations certain globular structures with short pedicles 6–8 microns in diameter. These, and some "terminal conidia" often contained several highly refractile spherical bodies, 0.5–1 micron in diameter. The authors suggest that these were perhaps ascospores, but there is no mention of any effort made to ascertain whether this was actually the case. I have observed similar bodies, but was unsuccessful in my attempts to find them in stained preparations.

By far the most interesting and important findings were in the tissues. For the present purpose it will not be necessary to enter into a detailed description of the lesions, and I shall confine myself to a discussion only of those points which bear on the present issue. The organism as found within the tissues is a spherical body varying in diameter from 3 or 4 to about 60 microns. All the smaller bodies and some of the largest are strongly gram-positive. The smaller bodies are spherical or slightly reniform, and do not possess a capsule. They are found lying free in the lymph spaces, and occasionally in capillaries. Sometimes one or more small bodies are found within a cell, apparently a macrophage. They occur singly or in groups numbering up to 15, 20, or more. In the larger groups the size of the individual bodies varies within very wide limits, from the smallest to the largest sizes being observed in the same group. Budding forms, clearly recognizable as such, are exceedingly rare.

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[1] *Jour. Infect. Dis.*, 1906, 3, p. 665.

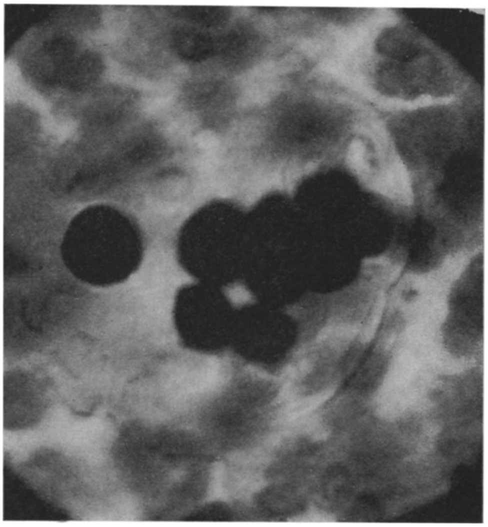

FIG. 6.—Same as Fig. 5, except the sac is occupied only by a few partly grown spores and leukocytes.

As the bodies attain full size a capsule appears about certain of them, consisting of a dense, non-staining membrane about 10 microns thick. The greater number of these membranes appear to be perfectly homogeneous, but in a certain number indications of an imperfect and somewhat irregular lamination can be made out.

Within the capsule the body may be either homogeneous, like the non-encapsulated forms, or, more rarely, condensations of chromatin at two or three points can be made out, with a thinning of the same in the intervening areas. The points of condensation are approximately the same size as the spores next to be described. The intervening steps between this stage and the fully developed ripe ascus have not been observed. The ascus consists of a capsule as above described, round or slightly oval, within which are found a large number of monocellular spores up to 50 or more, approximately 7 microns in diameter, round or slightly reniform, and lying closely packed in the sac. It is obviously impossible to make an accurate count of the number in a cross-section of the ascus, or to determine whether the number is the same in all cases, when the number is so large. This point cannot be determined until a culture medium is found, on which the plant will grow freely and produce its fruit in characteristic fashion. It is curious that no one seems to have tried growing the plant in the natural habitat of the fungi to which it appears to be most closely related. In all probability it does not belong to the saprophytic molds in the series, since in this case it might be expected to grow readily to full maturity on the various laboratory media. It is my intention to observe its behavior during the coming summer as a parasite on the

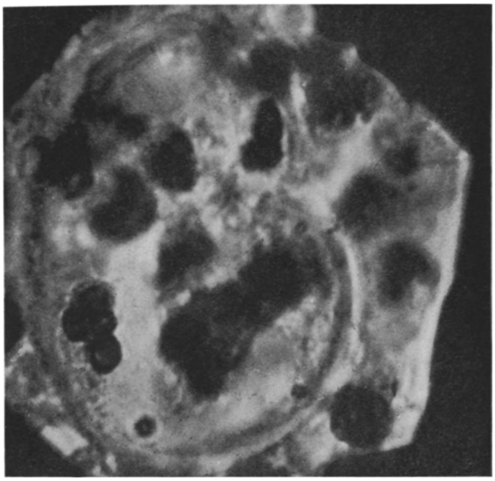

FIG. 7.—Same as Fig. 5. Sac empty save for a few leukocytes, not in perfect focus, and a few red cells.

various plants known to be subject to disease caused by similar organisms. Should these experiments prove successful, it may afford a final solution of the problem of its true botanical position, and at the same time give us the means for arriving at an adequate prophylaxis.

The further development of the asci can be traced in the tissues without difficulty. At a certain stage the ascus ruptures, and the spores are discharged into the neighboring tissue. Here they lie free for a time, and enlarge, but with unequal rapidity, so that, as already noted, groups of spores contain individuals of every size from the smallest to the largest. Some are taken up by leukocytes (macrophages) and are carried to lymph vessels or blood capillaries, or, apparently, they may find their way to either of these destinations without being taken up. Giant cells form about them, either inside or outside the vessel. The empty capsule which remains is also attacked by leukocytes, and is no doubt ultimately destroyed by them.

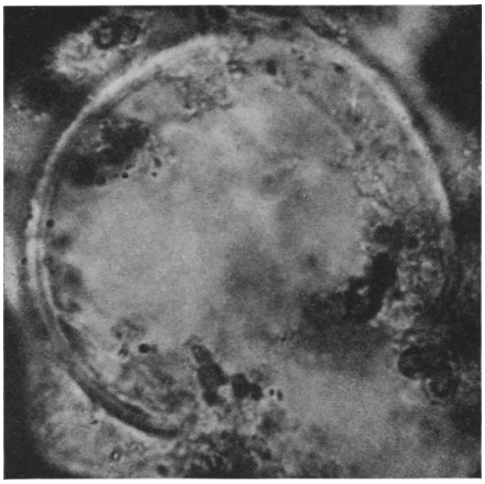

FIG. 8.—Same as Fig. 5. Sac empty.

I may add here that I have also observed in this case, so far as I know for the first time, the production of mycelium within the tissues. In only one field have I encountered an unmistakable mass of mycelium somewhat resembling the "sulfur granule" of actinomycosis. In several instances, however, I have observed spores from which distinct mycelial threads can be traced for a short distance.

As already stated, De Beurmann and Gougerot have followed the mycologic system of Van Tieghem, but I am advised that the much later system of Engler and Prantl[1] is now generally accepted by mycologists as authoritative, and I therefore follow the latter even at the risk of further complicating the question.

Table I, which is based on Engler and Prantl, gives the type characters of the various organisms with which the blastomyces may possibly belong. Certain differences in detail between the two systems of classification will be discussed more fully later.

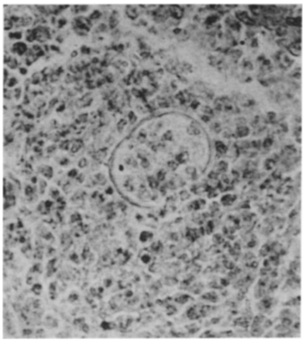

FIG. 9.—Low magnification (about 700×). Ascus empty of spores, and in course of invasion by leukocytes.

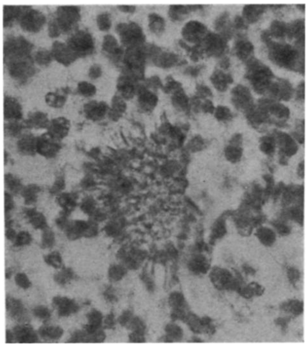

FIG. 10.—Low magnification (about 700×). Small mass of tangled mycelial threads.

This classification of Engler and Prantl shows certain important differences from that used by De Beurmann and Gougerot. The Exoascaceae are not included under the discomycetes, nor in the same family with the Protoascineae, which includes the saccharomyces and endomyces. In accordance with this classification the organism may be a variety of either of two species, which are, moreover, rather widely separated. The definition of the species *Monascus* of the genus *Monascaceae,* of the family Hemiascineae fits the findings save for the perithecium consisting of tangled mycelial threads. But the "irregular and imperfect lamination" already referred to may prove to be such a perithecium. On the

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[1] *Natürliche Pflanzenfamilien,* Teil 1, Abteilung 1, p. 142, Leipzig, 1897.

TABLE 1.

ASCOMYCETES.

A. HEMIASCEAE. Asci contain many spores, number indefinite.
  1. Hemiascineae.
    a) *Ascoideaceae.* Sporangia long, hose-like. Conidia present. { Ascoidea. Dipodascus.
    b) *Protomycetaceale.* Sporangia ellipsoid or round. Conidia unknown. { Protomyces, parasitic. Endogona, saprophytic.
    c) *Monascaceae.* Sporangia have more or less well developed capsule. *Monascus*, sporangium many spored, covered by tangled hyphae, forming a capsule.

B. EUASCEAE. Asci with typical constant number of spores, a power of 2.
  1. Protoascineae. Asci entirely disjoined, or formed at various heights on the mycelial threads.
    a) *Saccharomycetaceae.* Vegetative cells single or loosely bound by budding process.
      Usually no hyphae, asci resemble vegetative cells. { Saccharomyces. Monospora.
    b) *Endomycetaceae.* Vegetative cells form a threadlike mycelium. Asci at ends of mycelial threads, rarely intercalary, sharply differentiated from the mycelium. {
      Podocapsa. Mycelium scantily developed.
      Eramascus. Asci formed by copulation of spirally wound hyphae.
      Endomyces. Asci asexual, 4-spored.
      Oleina. Asci asexual, 8-spored.
  2. Protodiscineae. Asci standing side by side, so as to form a hymenium, which lacks clearly defined borders.
    a) *Exoascaceae.* Mycelium parasitic. Asci free from one another, protruding immediately from the substrat, without clearly defined hypothecium. {
      Magnusiella. Asci terminal.
      Exoascus. Ascus springs from a subcuticular ascogenic mycelial membrane. Asci 8-, or rarely 4-spored.
      Taphria, like Exoascus, except ascus contains large number of spores produced by budding of spores within the ascus.
    b) *Ascocorticaceae.* Mycelium saphophytic. Asci standing close together upon a cuticular hypothecium.
  3. Discomycetes. Helvellineae, mycelium well developed but insignificant as compared with the strongly developed fruit bodies. Fruit bodies club, hat, or scab shaped, fleshy, waxy, or more rarely, gelatinous. Hymenium spread out superficially, from the earliest stages free, circumscribed, resting upon a definite hypothallus, and consisting of asci and paraphyses standing close together.

other hand, it closely resembles the species *Taphria*, of the family Exoascaceae which it seems to resemble even more closely than it does *Monascus*. It is hoped that future observations will render possible a definite settlement of this question. If it proves to be a variety of *Taphria*, the classification proposed by De Beurmann and Gougerot will have been fully confirmed. In this connection it may be noted that occasionally one finds groups of the smallest, and presumably therefore only recently liberated spores, broken up into still smaller bodies, sometimes with tiny processes. Such a group of budding (?) spores suggests very strongly the appearance of a splash of water which has been thrown forcibly on the floor. If I am right in interpreting these groups as instances of multiplication of the spores by budding, we have an added argument for including the organism with the Taphriae.

CONCLUSIONS.

1. The organism of blastomycosis is an ascus-producing fungus. The ascus when ripe contains a large number (40 or more) of monocellular spores. It is not yet determined whether the number is or is not constant.
2. On the basis of present knowledge the plant may belong either to the Hemiasceae genus *Monascaceae*, or to the Euasceae group *Exoascaceae*, species *Taphria*. In the latter case, the view of De Beurmann and Gougerot becomes established, except in the matter of its close relationship of saccharomyces and endomyces, a difference which depends on the system of classification employed.
3. The name suggested by De Beurmann and Gougerot, namely, *Zymonema*, may be accepted, unless further observation should result in identifying the organism with some older member of one or the other orders above mentioned.
4. There is reason to hope that a study of the behavior of the organism under the conditions of life known to be natural to other members of the above groups may afford important and even complete information regarding its botanical position.
5. The final solution of the questions involved would render possible the recognition of the mold in its natural habitat as a plant pathogenic for man and certain animals, and would thus establish prophylaxis against the disease.